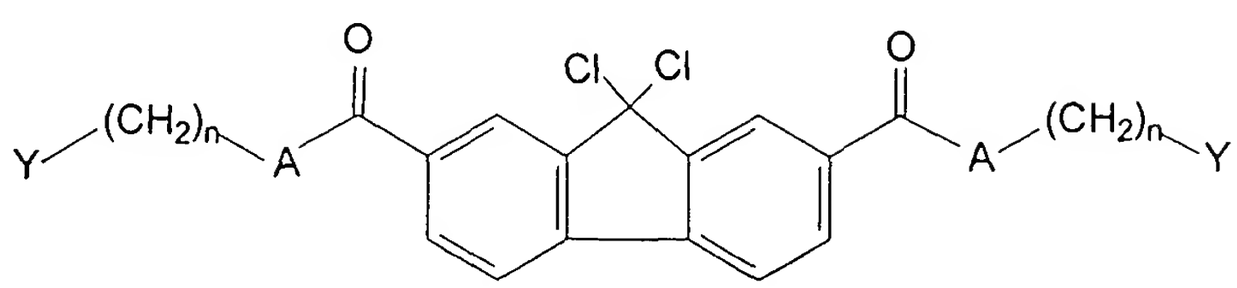
CLAIMS

What is claimed is:

1. A compound of the Formula I:



I

wherein:

A is CH_2, O, or S;

n is 0 to 4; and

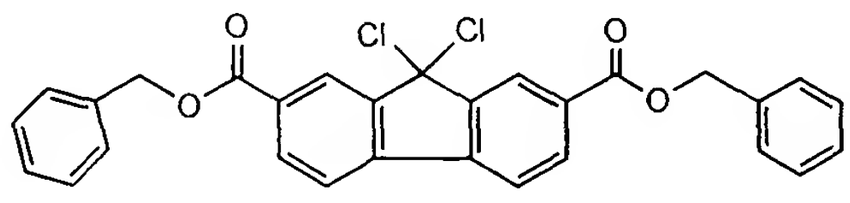
Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

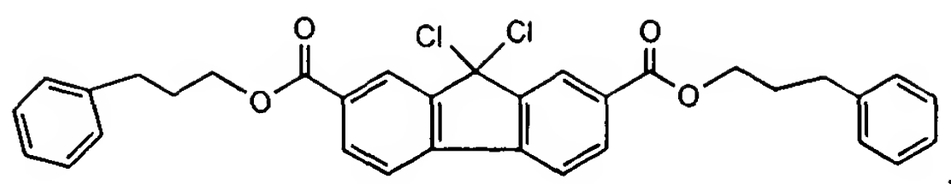
2. A compound, prodrug, metabolite, or salt according to claim 1, wherein:

A is O; n is 0-4; and Y is a substituted or unsubstituted aryl.

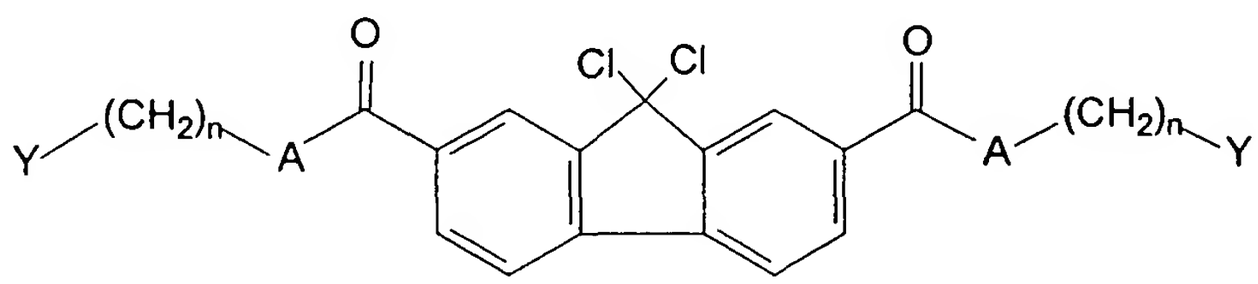
3. A compound, prodrug, metabolite, or salt according to claim 2 selected from:



, and



4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula I:



I

wherein:

A is CH_2, O, or S;

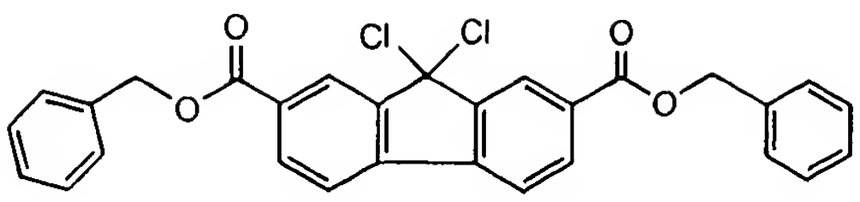
n is 0 to 4; and

Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

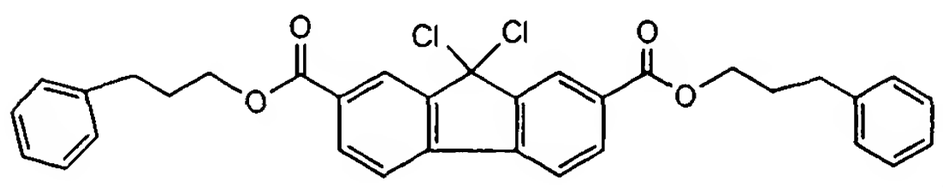
or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

5. The pharmaceutical composition according to claim 4, wherein: A is O; n is 0-4; and Y is a substituted or unsubstituted aryl.

6. The pharmaceutical composition according to claim 5, wherein the compound is selected from:



, and



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7. The composition according to claim 4, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

8. The composition according to claim 4, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

9. The composition according to claim 4, wherein the composition is a solid implant.

10. The composition according to claim 4, wherein the carrier comprises a biodegradable polymer.

11. The composition according to claim 10, wherein the biodegradable polymer releases the compound of formula I over a prolonged time.

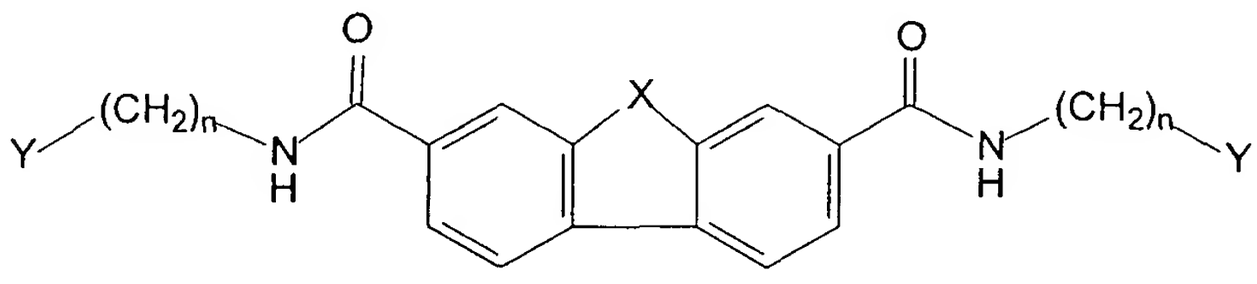
12. A method of modulating or inhibiting PARG by administering a compound of Formula I according to claim 1, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral

nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

13. The method according to claim 12 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

14. The method according to claim 13 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

15. A compound of Formula II



II

wherein:

x is C=O, CH_2, or $C(Cl)_2$;

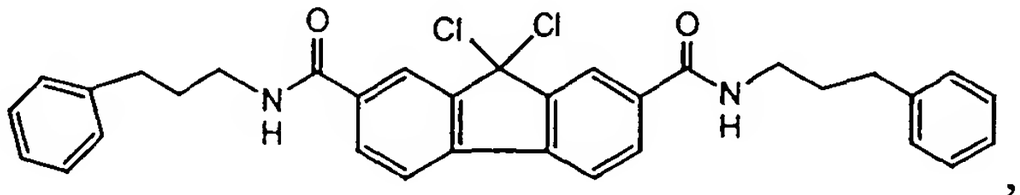
n is 0 to 4; and

Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

16. A compound, prodrug, metabolite, or salt according to claim 15, wherein: x is C=O or $C(Cl)_2$; n is 0 to 4; and Y is a substituted or unsubstituted aryl.

17. A compound, prodrug, metabolite, or salt according to claim 16 selected from: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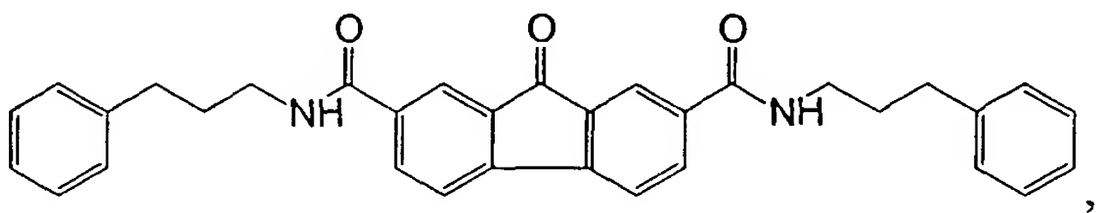
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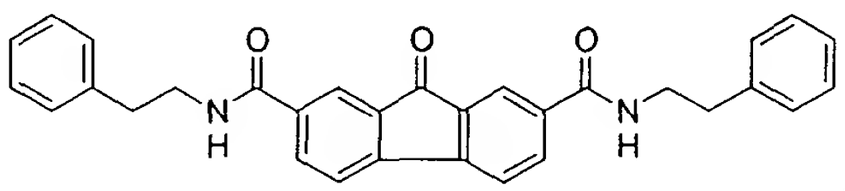
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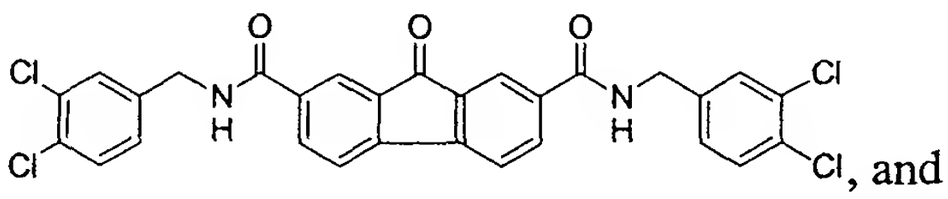
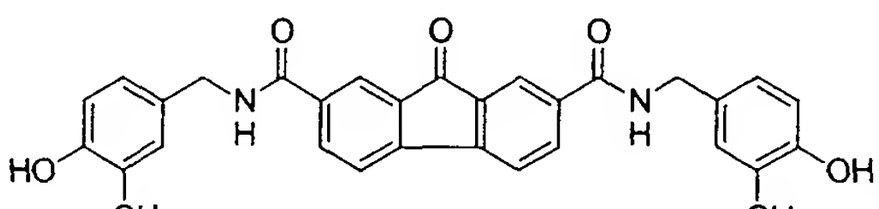

, and

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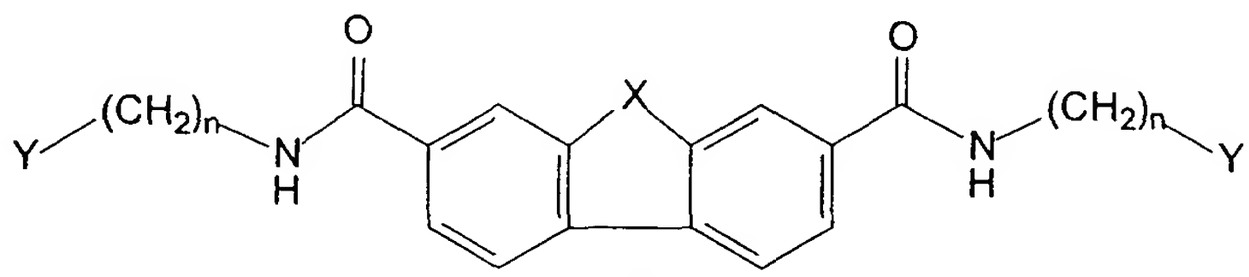
18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula II:



II

wherein:

x is C=O, CH_2, or $C(Cl)_2$;

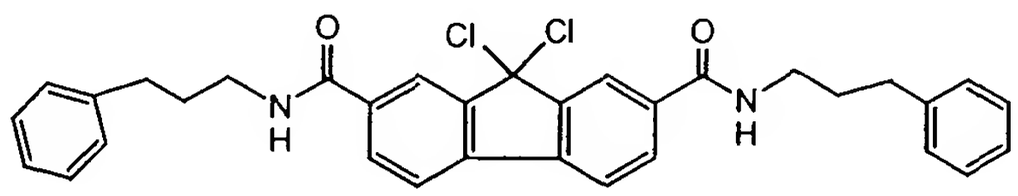
n is 0 to 4; and

Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

19. The pharmaceutical composition according to claim 18, wherein: x is C=O or $C(Cl)_2$; n is 0 to 4; and Y is a substituted or unsubstituted aryl.

20. The pharmaceutical composition according to claim 19 selected from:



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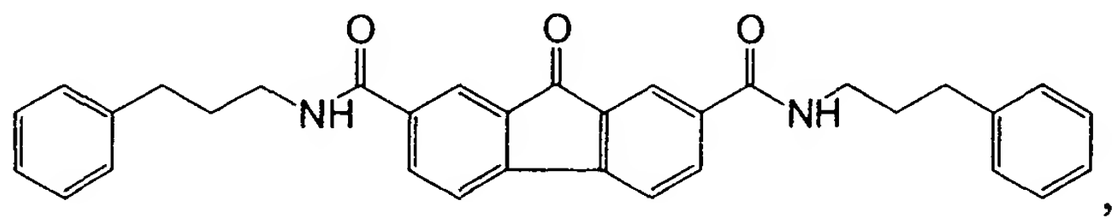

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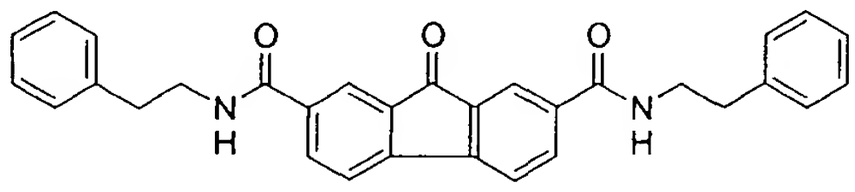

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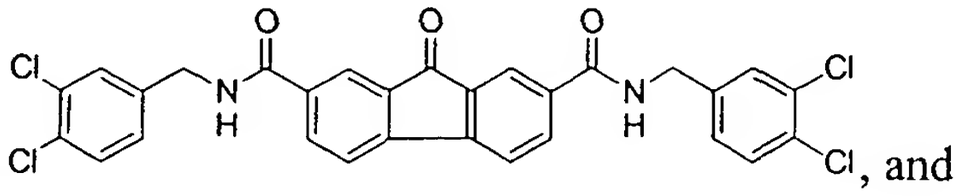
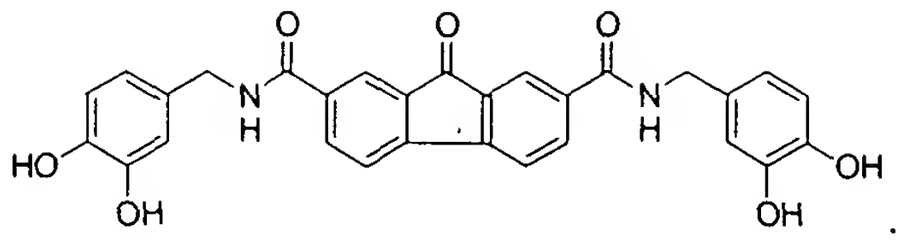


, and



21. The composition according to claim 18, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

22. The composition according to claim 18, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

23. The composition according to claim 18, wherein the composition is a solid implant.

24. The composition according to claim 18, wherein the carrier comprises a biodegradable polymer.

25. The composition according to claim 24, wherein the biodegradable polymer releases the compound of formula II over a prolonged time.

26. A method of modulating or inhibiting PARG by administering a compound of Formula II according to claim 15, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative

capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

27. The method according to claim 26 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

28. The method according to claim 27 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

29. A method of treating or preventing diseases or conditions resulting from cell damage or death comprising administering to an animal a therapeutically effective amount of a compound of Formula II according to claim 15, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

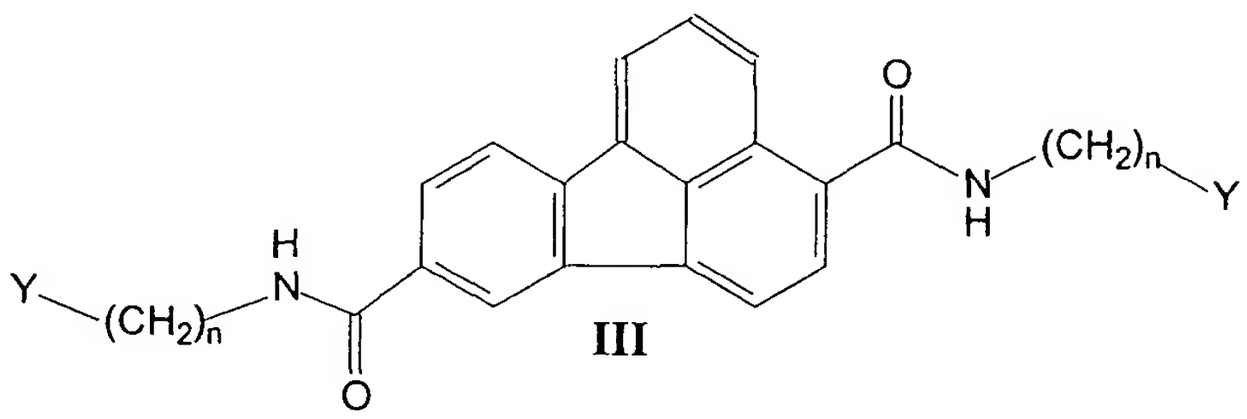
30. The method according to claim 29 wherein the diseases or conditions are selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke,

diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

31. The method according to claim 30 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

32. The method according to claim 31 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

33. A compound of the Formula III:



III

wherein:

n is 0 to 4; and

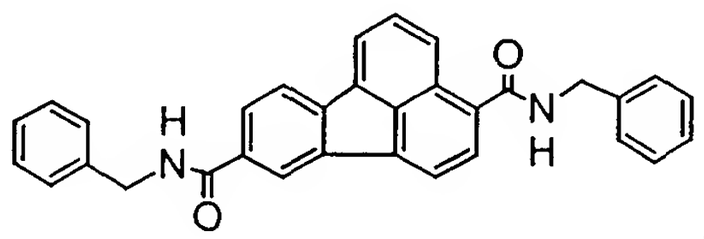
Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubtituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

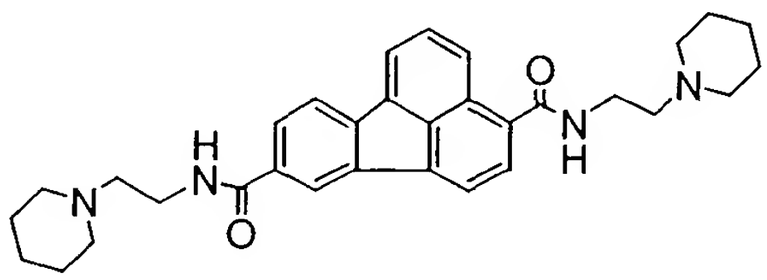
34. A compound, prodrug, metabolite, or salt according to claim 33, wherein:

n is 0 to 4; and Y is a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are taken together to form a substituted or unsubstituted five or six membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S.

35. A compound, prodrug, metabolite, or salt according to claim 34 selected from:



, and



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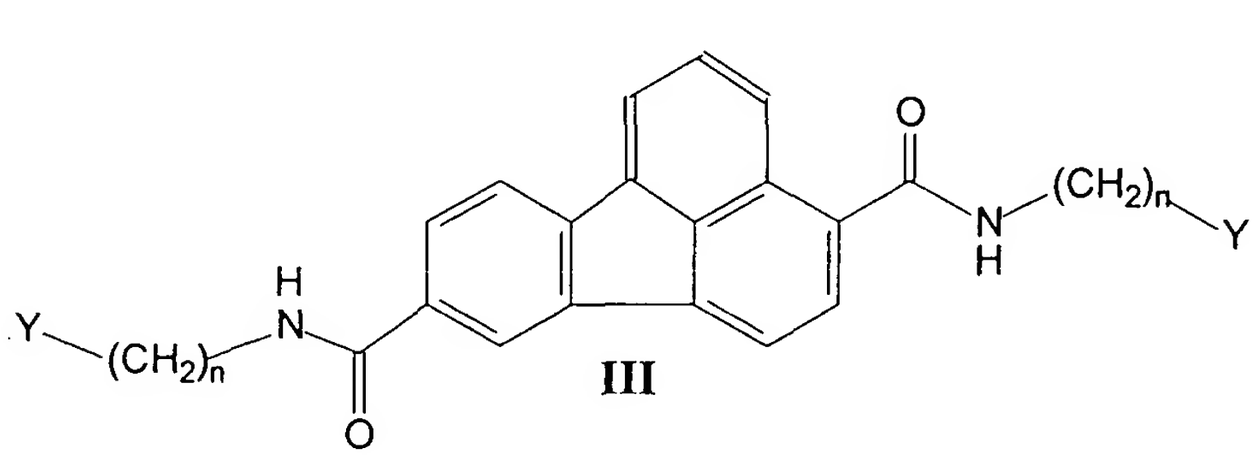
36. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula III:



III

wherein:

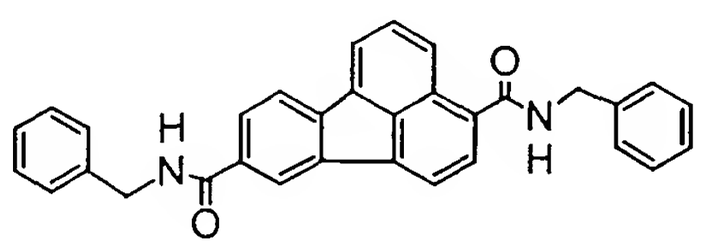
n is 0 to 4; and

Y is hydrogen, or a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubtituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

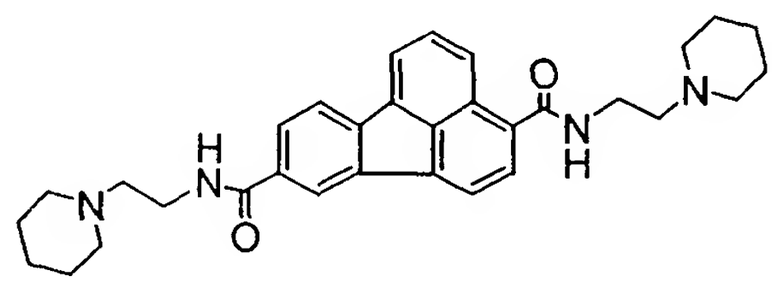
or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

37. The pharmaceutical composition according to claim 36, wherein: n is 0 to 4; and Y is a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl, or $N(R^1)(R^2)$, wherein R^1 and R^2 are taken together to form a substituted or unsubstituted five or six membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S.

38. The pharmaceutical composition according to claim 37 selected from:



, and



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39. The composition according to claim 36, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

40. The composition according to claim 36, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

41. The composition according to claim 36, wherein the composition is a solid implant.

42. The composition according to claim 36, wherein the carrier comprises a biodegradable polymer.

43. The composition according to claim 42, wherein the biodegradable polymer releases the compound of formula III over a prolonged time.

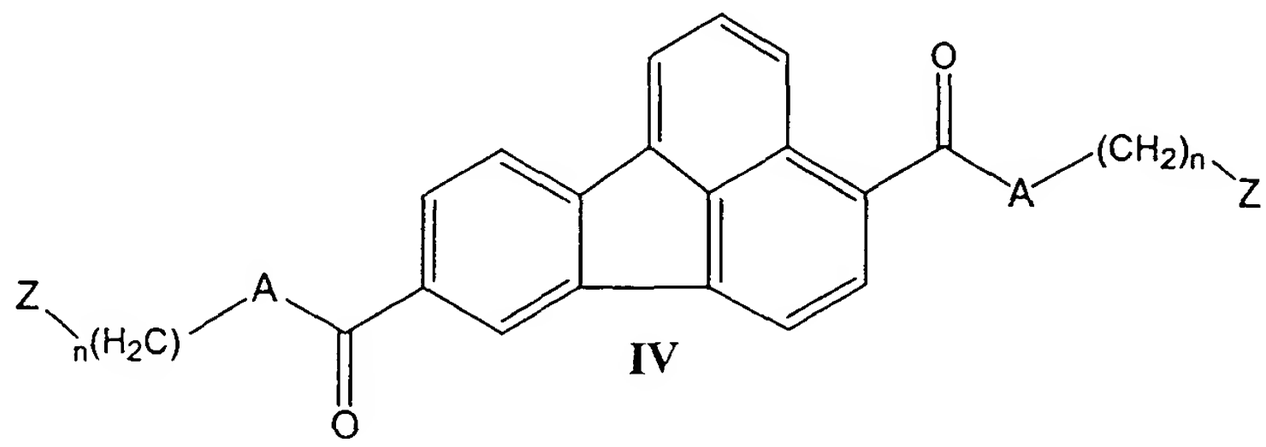
44. A method of modulating or inhibiting PARG by administering a compound of Formula III according to claim 33, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

45. The method according to claim 44 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal

ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

46. The method according to claim 45 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

47. A compound of the Formula IV:



IV

wherein:

n is 0 to 4;

A is CH_2, O, or S; and

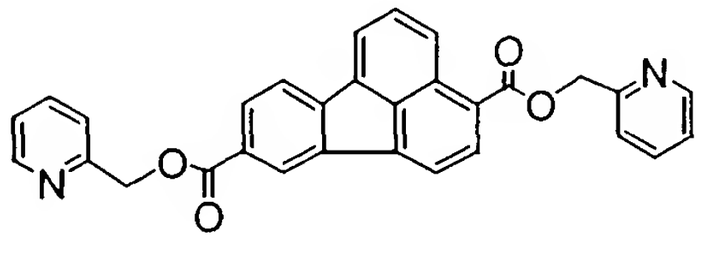
Z is a substituted or unsubstituted aryl or heteroaryl, or $N(R^3)(R^4)$, wherein R^3 is a substituted or unsubstituted aryl or heteroaryl, and R^4 is hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^3 and R^4 are taken together to form a substituted or unsubstituted five to six membered aromatic ring;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

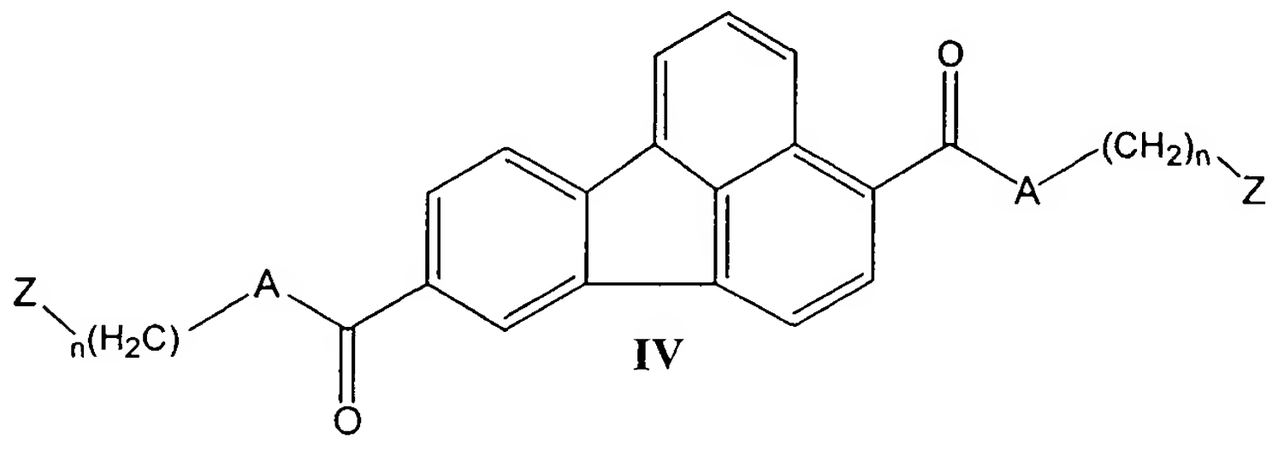
48. A compound, prodrug, metabolite, or salt according to claim 47, wherein: n is 1 to 3; A is CH_2 or O; and Z is a substituted or unsubstituted aryl or heteroaryl, or $N(R^3)(R^4)$, wherein R^3 is a substituted or unsubstituted aryl or heteroaryl, and R^4 is a

substituted or unsubstituted lower alkyl, or R^3 and R^4 are taken together to form a substituted or unsubstituted five to six membered aromatic ring.

49. A compound, prodrug, metabolite, or salt according to claim 48 selected from:



50. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula IV:



IV

wherein:

n is 0 to 4;

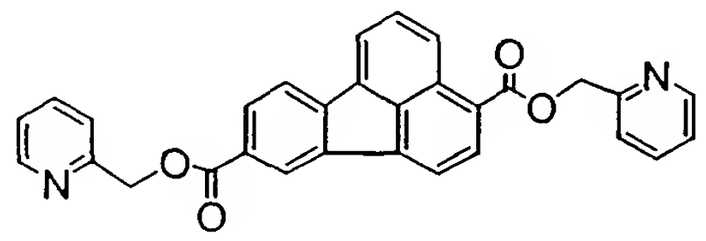
A is CH_2, O, or S; and

Z is a substituted or unsubstituted aryl or heteroaryl, or $N(R^3)(R^4)$, wherein R^3 is a substituted or unsubstituted aryl or heteroaryl, and R^4 is hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^3 and R^4 are taken together to form a substituted or unsubstituted five to six membered aromatic ring;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

51. The pharmaceutical composition according to claim 50, wherein: n is 1 to 3; A is CH_2 or O; and Z is a substituted or unsubstituted aryl or heteroaryl, or $N(R^3)(R^4)$, wherein R^3 is a substituted or unsubstituted aryl or heteroaryl, and R^4 is a substituted or unsubstituted lower alkyl, or R^3 and R^4 are taken together to form a substituted or unsubstituted five to six membered aromatic ring.

52. The pharmaceutical composition according to claim 51, wherein the compound is selected from:



53. The composition according to claim 50, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

54. The composition according to claim 50, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

55. The composition according to claim 50, wherein the composition is a solid implant.

56. The composition according to claim 50, wherein the carrier comprises a biodegradable polymer.

57. The composition according to claim 56, wherein the biodegradable polymer releases the compound of formula IV over a prolonged time.

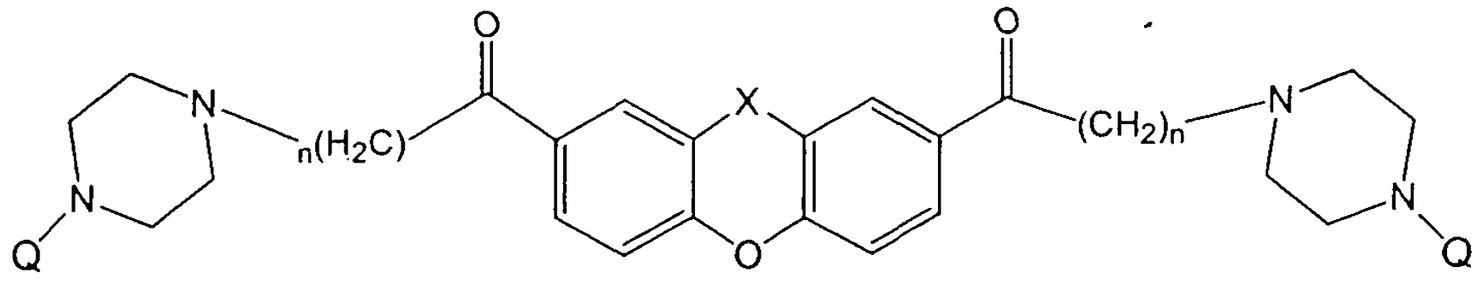
58. A method of modulating or inhibiting PARG by administering a compound of Formula IV according to claim 47, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or

metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

59. The method according to claim 58 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

60. The method according to claim 59 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

61. A compound of the Formula V:



V

wherein:

x is C=O, CH_2, or $C(Cl)_2$;

n is 0 to 4; and

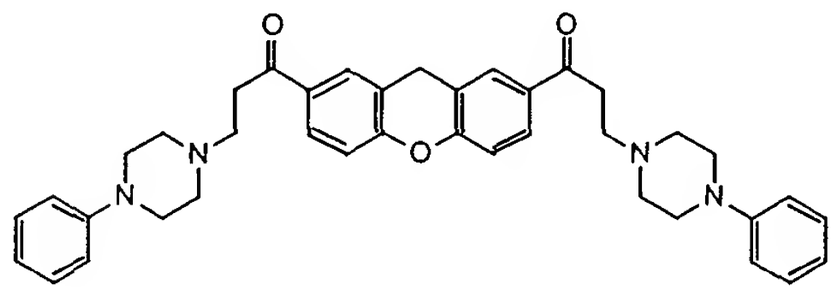
Q is a substituted or unsubstituted aryl or heteroaryl;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

62. A compound, prodrug, metabolite, or salt according to claim 61, wherein:

n is 2; x is C=O or CH_2; and Q is a substituted or unsubstituted aryl.

63. A compound, prodrug, metabolite, or salt according to claim 62 selected from:



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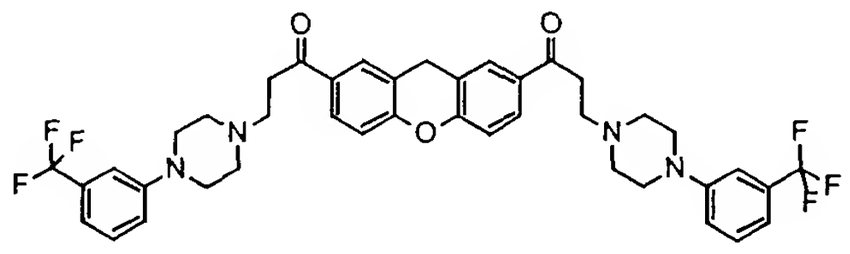

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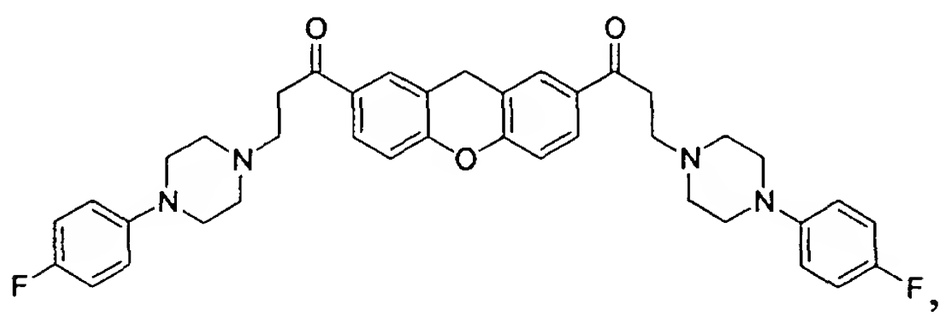
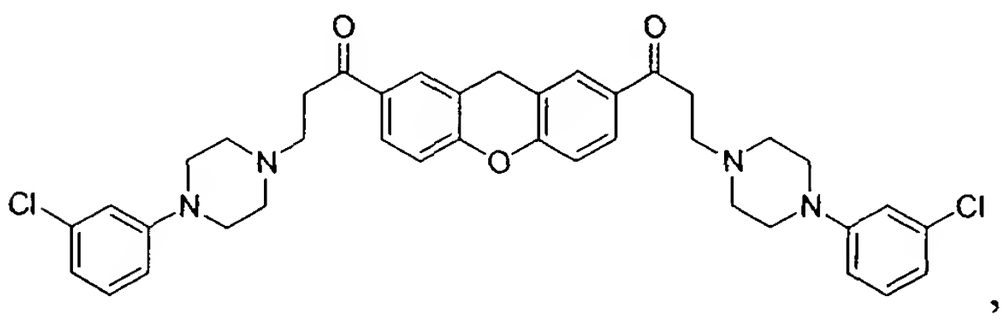


,



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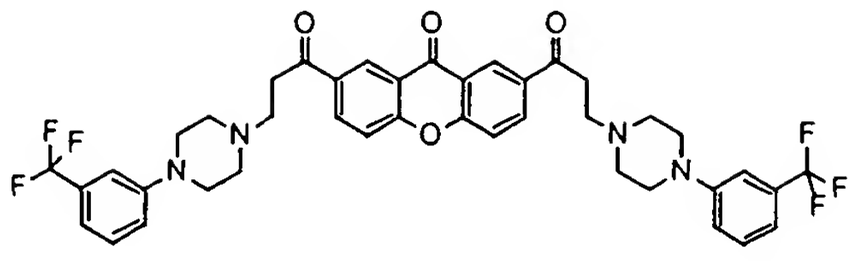
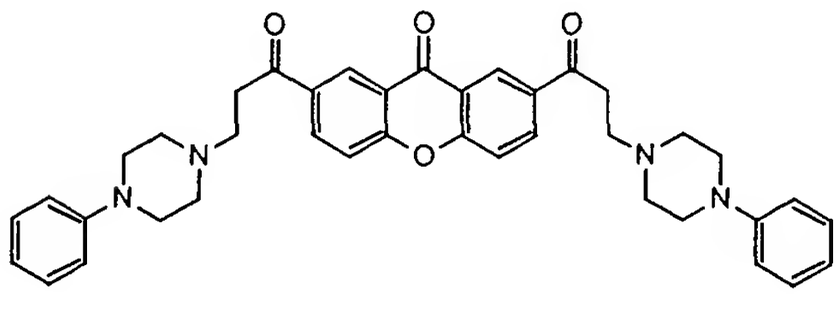


, and



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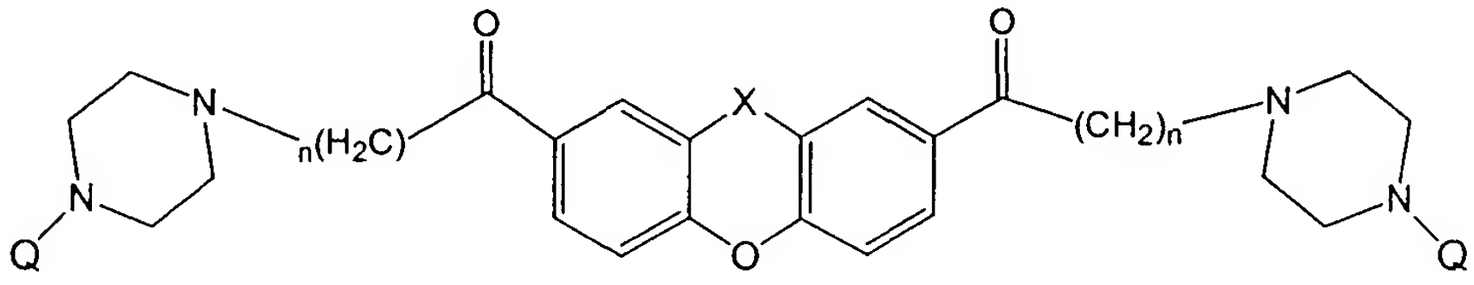
64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula V:



V

wherein:

x is C=O, CH_2, or $C(Cl)_2$;

n is 0 to 4; and

Q is a substituted or unsubstituted aryl or heteroaryl;

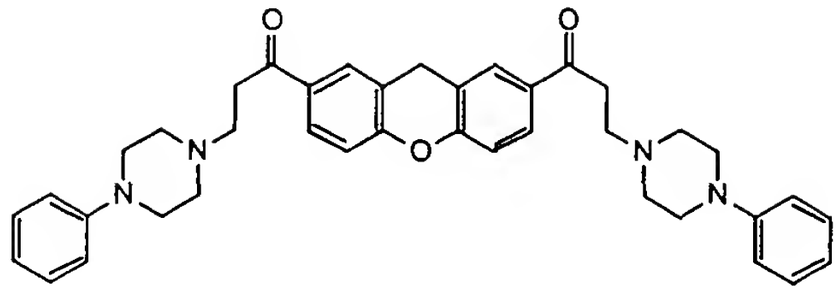
or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

65. The pharmaceutical composition according to claim 64 wherein: n is 2; x is C=O or CH_2; and Q is a substituted or unsubstituted aryl.

66. The pharmaceutical composition according to claim 65 selected from:

)

)



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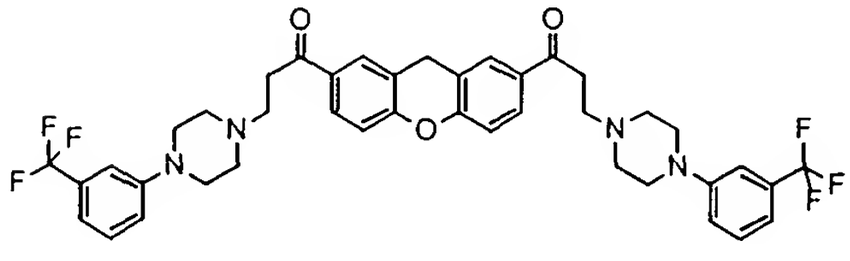

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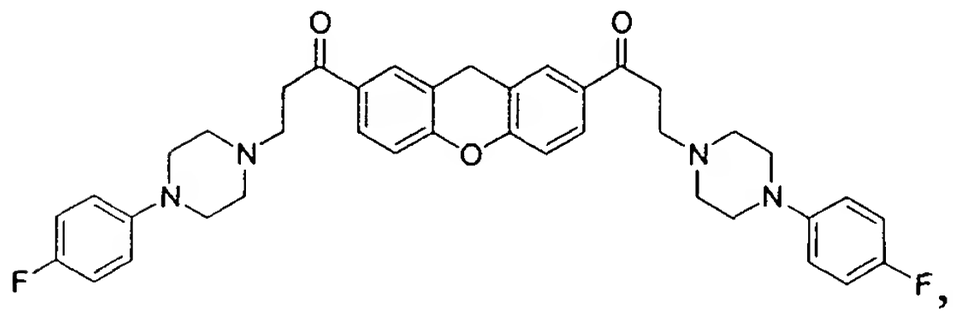

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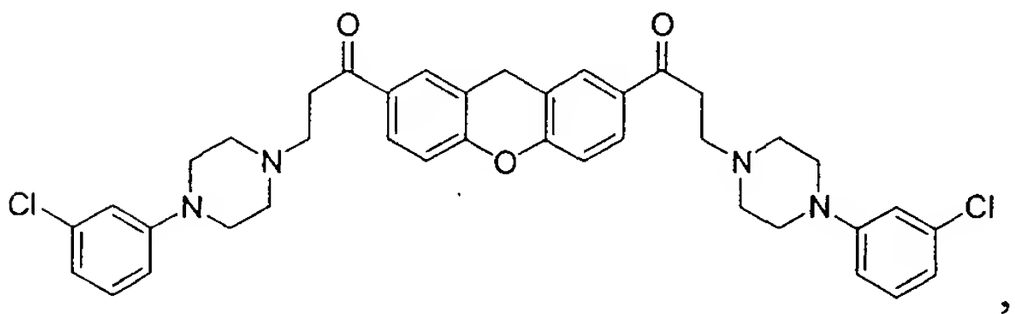

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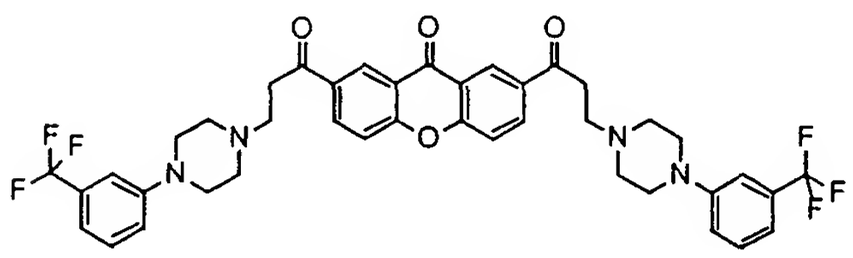
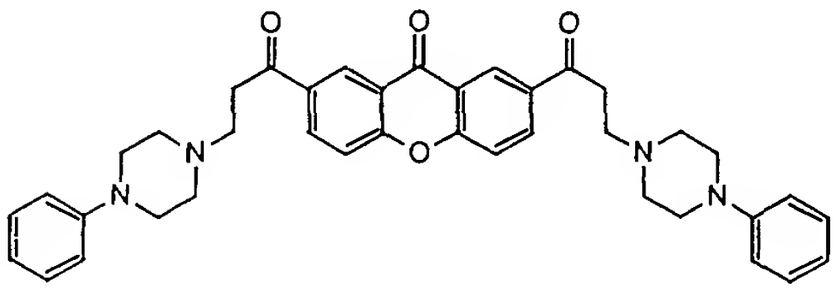


, and



.

67. The composition according to claim 64, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

68. The composition according to claim 64, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

69. The composition according to claim 64, wherein the composition is a solid implant.

70. The composition according to claim 64, wherein the carrier comprises a biodegradable polymer.

71. The composition according to claim 70, wherein the biodegradable polymer releases the compound of formula V over a prolonged time.

72. A method of modulating or inhibiting PARG by administering a compound of Formula V according to claim 61, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

73. The method according to claim 72 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting

from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

74. The method according to claim 73 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

75. A method of treating or preventing diseases or conditions resulting from cell damage or death comprising administering to an animal a therapeutically effective amount of a compound of Formula V according to claim 61, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

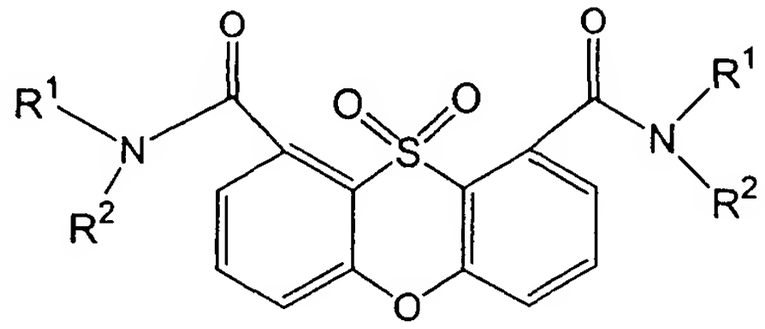
76. The method according to claim 75 wherein the diseases or conditions are selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

77. The method according to claim 76 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases,

neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

78. The method according to claim 77 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

79. A compound of the Formula VI:



VI

wherein:

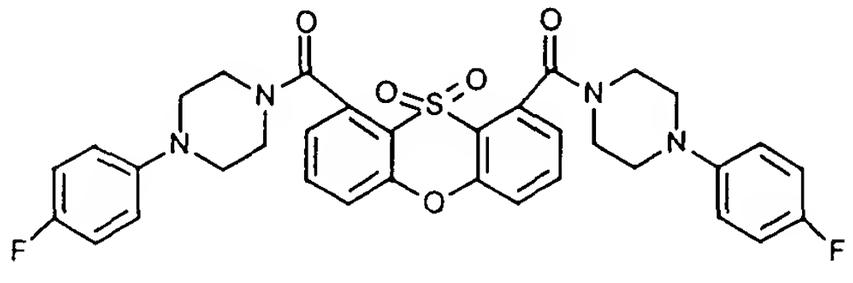
R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

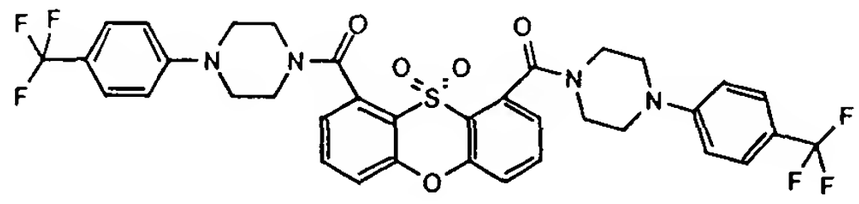
80. A compound, prodrug, metabolite, or salt according to claim 79, wherein:

R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, or R^1 and R^2 are taken together to form a substituted or unsubstituted six membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S.

81. A compound, prodrug, metabolite, or salt according to claim 80 selected from:



, and



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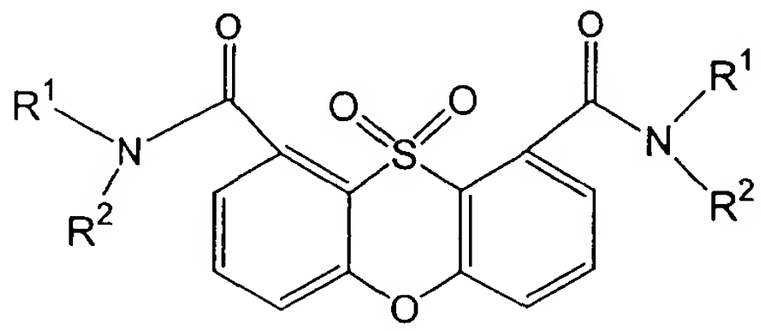
82. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula VI:



VI

wherein:

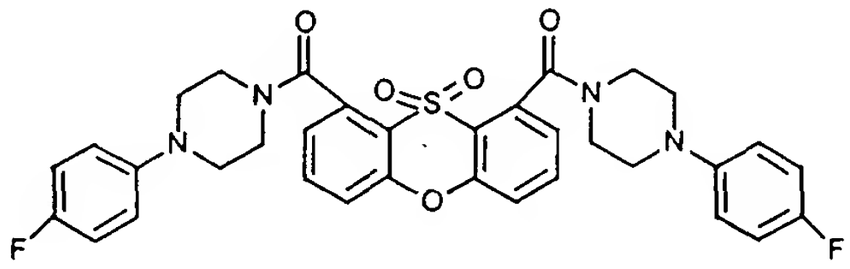
R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^1 and R^2 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

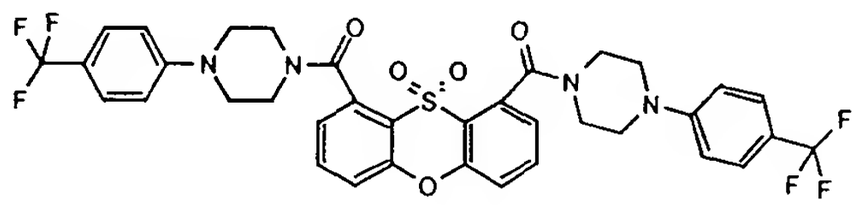
83. The pharmaceutical composition according to claim 82, wherein:

R^1 and R^2 are independently hydrogen, a substituted or unsubstituted lower alkyl, or R^1 and R^2 are taken together to form a substituted or unsubstituted six membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S.

84. The pharmaceutical composition according to claim 83 selected from:



, and



.

85. The composition according to claim 82, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

86. The composition according to claim 82, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

87. The composition according to claim 82, wherein the composition is a solid implant.

88. The composition according to claim 82, wherein the carrier comprises a biodegradable polymer.

89. The composition according to claim 88, wherein the biodegradable polymer releases the compound of formula VI over a prolonged time.

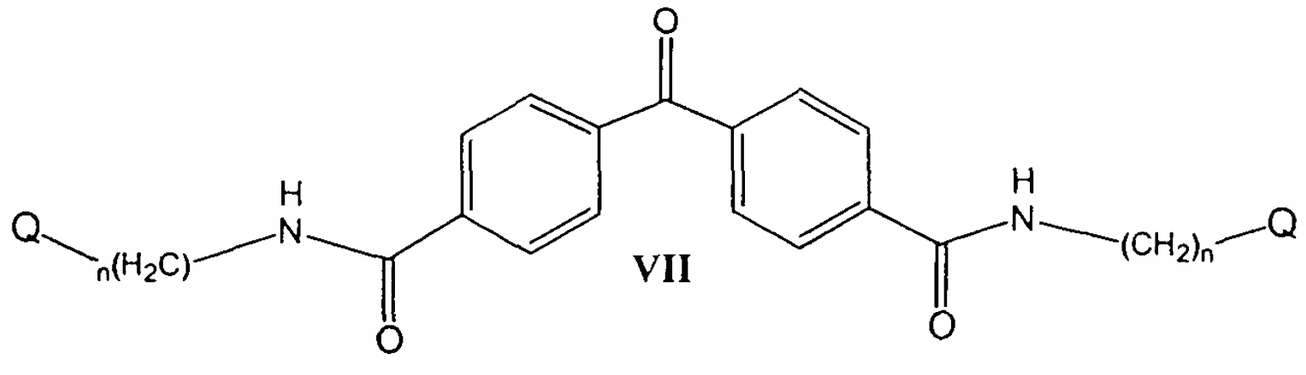
90. A method of modulating or inhibiting PARG by administering a compound of Formula VI according to claim 79, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or

metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

91. The method according to claim 90 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

92. The method according to claim 91 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.

93. A compound of the Formula VII:



VII

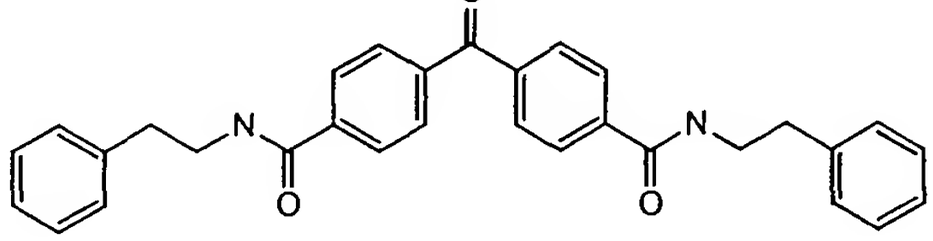
wherein:

n is 1 to 3; and

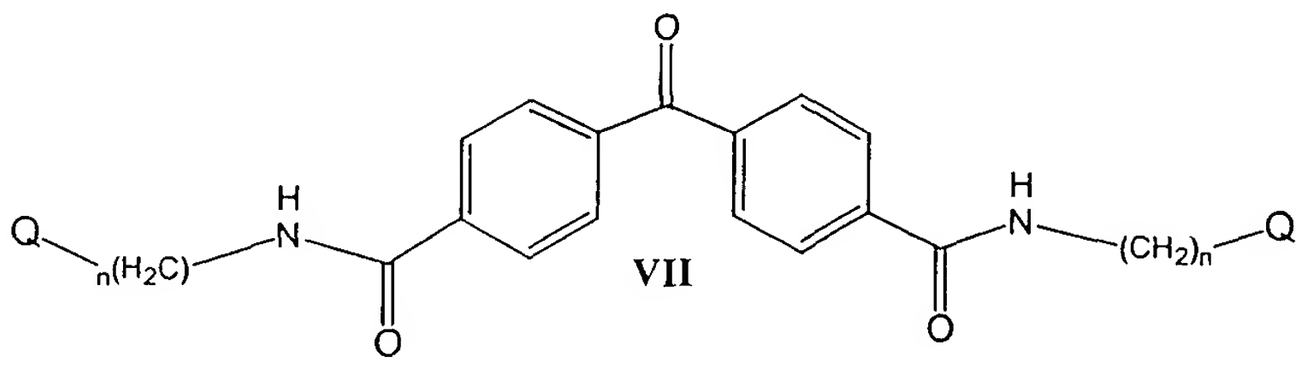
Q is a substituted or unsubstituted aryl or heteroaryl;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

94. A compound, prodrug, metabolite, or salt according to claim 93 selected from:



95. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula VII:



VII

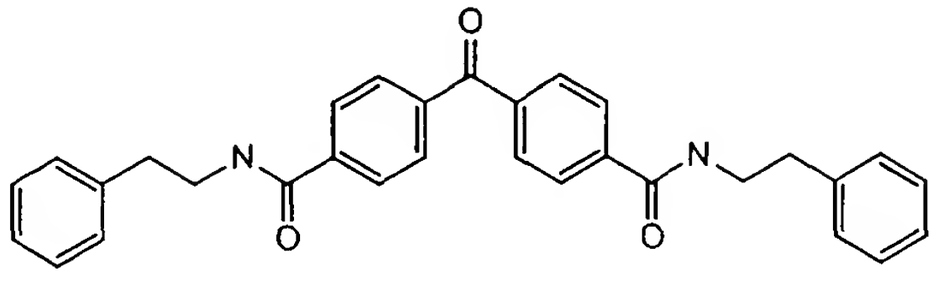
wherein:

n is 1 to 3; and

Q is a substituted or unsubstituted aryl or heteroaryl;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

96. The pharmaceutical composition according to claim 95 selected from:



97. The composition according to claim 95, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

98. The composition according to claim 95, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

99. The composition according to claim 95, wherein the composition is a solid implant.

100. The composition according to claim 95, wherein the carrier comprises a biodegradable polymer.

101. The composition according to claim 100, wherein the biodegradable polymer releases the compound of formula VII over a prolonged time.

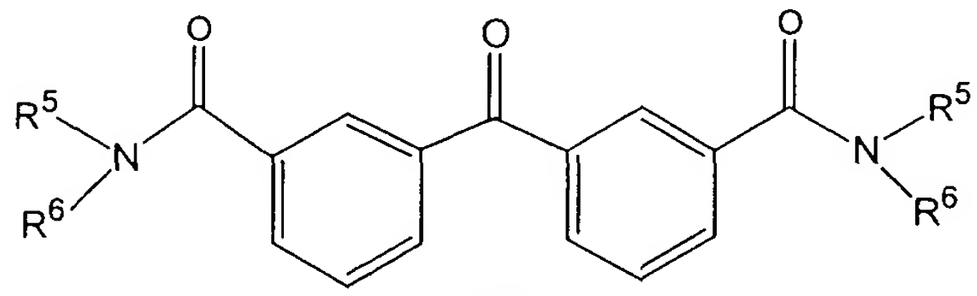
102. A method of modulating or inhibiting PARG by administering a compound of Formula VII according to claim 93, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic

k, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative city of cells, and diseases or disease conditions induced or exacerbated by cellular scence.

103. The method according to claim 102 wherein the diseases or conditions are cted from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage lting from ischemia and reperfusion injury, neurological disorders and neurodegenerative ases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve y, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or ferative capacity of cells.

104. The method according to claim 103 wherein the disease or condition is tissue age resulting from ischemia and reperfusion injury.

105. A compound of the Formula VIII:



VIII

ein:

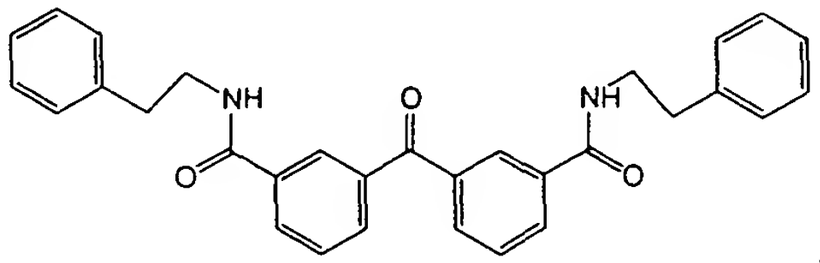
R^5 is hydrogen, and R^6 is a substituted or unsubstituted lower alkyl, lower alkenyl, ocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^5 and R^6 are taken together to a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1- eroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active polite of said compound, or pharmaceutically acceptable salt of said compound or polite.

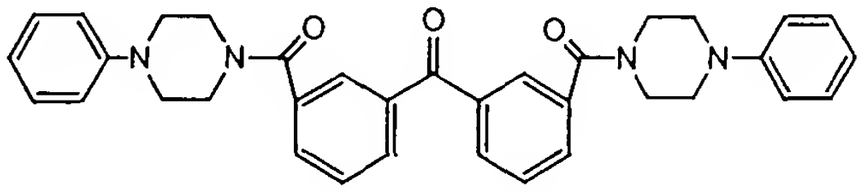
106. A compound, prodrug, metabolite, or salt according to claim 105, wherein:

R^5 is hydrogen, and R^6 is a substituted or unsubstituted lower alkyl, or R^5 and R^6 are taken together to form a substituted or unsubstituted six membered heterocyclic ring that contains 1-2 heteroatoms of N.

107. A compound, prodrug, metabolite, or salt according to claim 106 selected from:



, and



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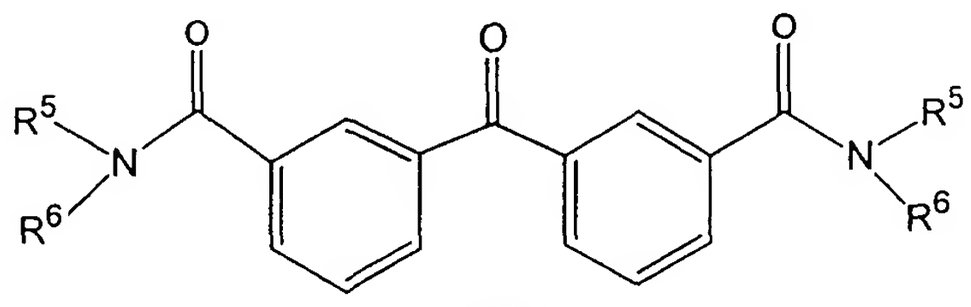
108. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula VIII:



VIII

wherein:

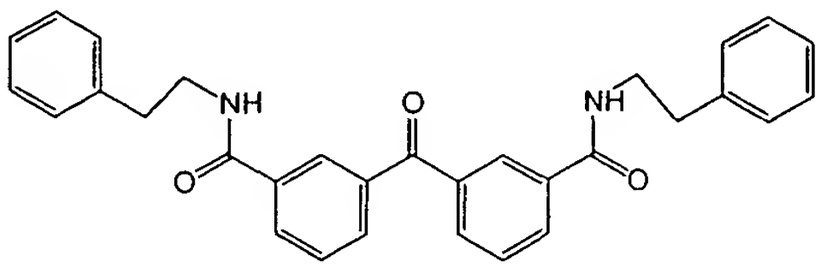
R^5 is hydrogen, and R^6 is a substituted or unsubstituted lower alkyl, lower alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylamino, arylamino, or R^5 and R^6 are taken together to form a substituted or unsubstituted five to seven membered heterocyclic ring that contains 1-3 heteroatoms of O, N, or S;

or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

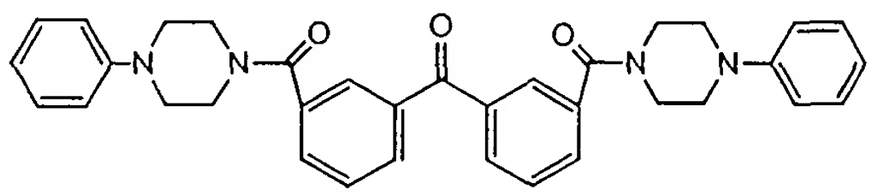
109. The pharmaceutical composition according to claim 108, wherein:

R^5 is hydrogen, and R^6 is a substituted or unsubstituted lower alkyl, or R^5 and R^6 are taken together to form a substituted or unsubstituted six membered heterocyclic ring that contains 1-2 heteroatoms of N.

110. The pharmaceutical composition according to claim 109 selected from:



, and



.

111. The composition according to claim 108, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

112. The composition according to claim 108, wherein said composition is administered as a capsule or tablet containing a single or divided dose of said compound.

113. The composition according to claim 108, wherein the composition is a solid implant.

114. The composition according to claim 108, wherein the carrier comprises a biodegradable polymer.

115. The composition according to claim 114, wherein the biodegradable polymer releases the compound of formula VIII over a prolonged time.

116. A method of modulating or inhibiting PARG by administering a compound of Formula VIII according to claim 105, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt of such compound or metabolite thereof, to treat diseases and disorders selected from acute pain, arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma, hyperglycemia, immune senescence, inflammatory bowel disorders, ischemia, macular degeneration, muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain, nervous insult, osteoarthritis, osteoporosis, peripheral nerve injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia, septic shock, skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

117. The method according to claim 116 wherein the diseases or conditions are selected from diabetes, head trauma, inflammatory bowel disorders, ischemia, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage disease, neuropathic pain, nervous insult, peripheral nerve injury, retinal ischemia, vascular stroke, and diseases or disorders relating to lifespan or proliferative capacity of cells.

118. The method according to claim 117 wherein the disease or condition is tissue damage resulting from ischemia and reperfusion injury.